



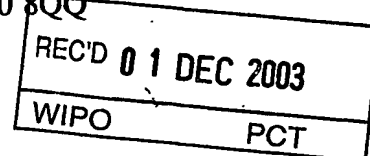
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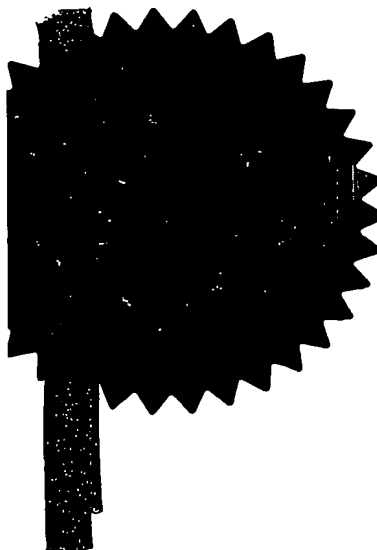
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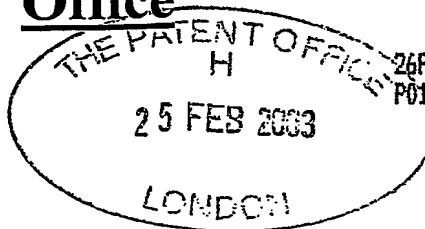
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3. Full name, address and postcode of the or of each applicant (underline all surnames)

GlaxoSmithKline Biologicals s.a.  
Rue de l'Institut 89, B-1330 Rixensart, Belgium

Patents ADP number (*if you know it*) 810 1271001

Belgian

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4. Title of the invention

Novel Device

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# Novel Device

This invention relates to a novel device, being a closure system for vials, particularly for pharmaceutical vials, i.e. for the sterile containment of drug substance or vaccine products therein.

Drug substance and vaccine products are frequently provided in vials which are closed with an elastomeric closure part through which a hollow needle can be passed, puncturing the closure part, and via which the drug substance or vaccine product may be extracted for use, optionally after reconstitution by an aqueous medium introduced into the vial via the needle. Normally such a vial has a mouth opening bounded by a flange-shaped rim, and the closure part is held in a closing relationship with the mouth opening by a flexible metal clamp part which surrounds the perimeter of the closure part and holds it tightly against the rim. Often a central area of the closure part may be punctured by the needle, and the clamp part has a removable central part, which prior to use covers this central area of the closure part, and which can be removed immediately before use. Often this central part is connected to peripheral parts of the clamp part by thin frangible links, enabling the central part to be initially connected to the peripheral parts and detached prior to use, giving tamper evidence. A problem with this known device is that it is difficult to achieve a sterile seal between the central part and closure part, so the user has to "sanitise" the central area of the closure part immediately prior to use, e.g. using an alcohol wipe.

It is also known, e.g. from US-A-2002/0023409, to provide a pharmaceutical vial having a closure part made of thermoplastic material. Such a vial can be filled using a hollow needle passed through the closure part, the needle is then withdrawn, and the small residual puncture hole may then be sealed by heat sealing, e.g. using a focussed laser beam.

It is an object of the present invention to provide a vial closure system which in part at least overcomes the above-mentioned problems of known closure systems, and is particularly suited to vial closures which can be heat-sealed after filling using a hollow needle, as described above. Other objects and advantages of the present invention will be apparent from the following description.

According to this invention, a closure system is provided for a vial of the type having an upwardly-facing mouth opening bounded by a rim, the closure system comprising:

an elastomeric closure part shaped to sealingly engage with the mouth opening, having a lower surface facing the interior of the vial and an opposite upper surface facing away from the vial, and capable of being punctured by a needle,

a clamp part able to engage with the vial, particularly with the rim of the mouth opening, and able to bear upon the upper surface of the closure part to hold the closure part in a closing relationship with the mouth opening,

the clamp part having an aperture therein through which a region of the upper surface of the closure part is exposed when the clamp part is engaged with the vial,

a cover part, engageable with the clamp part and/or the vial to cover the said region of the closure part, a lower surface of the cover part facing the upper surface of the closure part when so engaged and having a sealing ridge projecting therefrom to a sealing edge that follows a closed perimeter, so that when the cover part is engaged with the clamp part and/or the vial the sealing edge engages with the closure part to form an enclosure with the closure part, at least that part of the cover part which includes the sealing ridge being removable from engagement with the clamp part and/or the vial.

The terms "upward", "upper", "lower" etc. and derived directional terms are based on the normal configuration of a vial in a vertical orientation with the mouth uppermost, but of course are applicable to any orientation of the vial and the parts of the closure system.

The vial is preferably of the type having a neck immediately downward of the mouth opening, and having a rim in the form of a flange having upper and lower surfaces extending transverse to, preferably perpendicular to, the upper-lower axis. Such vials are well known in the pharmaceutical industry. Suitably the upper surface of the flange may be bounded by a peripheral upwardly-extending kerf edge. Suitably the upper surface of the flange may have an upwardly extending sealing ridge to engage against a downward facing surface of the closure part to improve sealing between the closure part and the flange. The vial may be made of

glass, or of a hard plastic material accepted for use in the pharmaceutical industry. An example of such a plastics material is the cyclolefin copolymer "Topas" made by Celanese Corporation.

5 The closure part preferably has a downwardly extending plug part which fits into the mouth opening of the vial, and an outwardly extending peripheral flange part, a downward facing surface of which can engage with the upward facing surface of a rim of the vial mouth opening in the form of a flange. Suitably the plug part has an outer perimeter which fits conformingly within the kerb of the flange. Upwardly of such a flange part the closure part may be flat but is preferably  
10 upwardly convex, e.g. domed or of a (frusto) conical shape. The plug part is suitably of a hollow cylindrical shape with an upper end of the hollow cylindrical interior extending into this upper domed or conical part.

Preferably at least the upper surface of the closure part adjacent to the said region, preferably an upper part, preferably the whole of the closure part is made of  
15 a thermoplastic elastomer material, so that a puncture hole formed as a result of filling the vial using a hollow needle may be sealed by thermal sealing, e.g. using a laser as described in US-A-2002.0023409. A suitable thermoplastic elastomer material is a 50:50 w:w blend of the polymers "Engage" supplied by Dupont-Dow, and "Dynaflex" formerly known as "Kraton" as supplied by Shell but now available  
20 from GLS (USA) who supply this blend, and including a dye, e.g. grey, to enhance absorption of laser light so that the elastomer material may be heated using laser light. Under irradiation from a focussed 980nm laser this polymer easily fuses at ca. 180°C and sets on cooling.

The clamp part is preferably made of a mouldable plastics material, and is  
25 able to engage with the vial, preferably being engageable with the above-mentioned flange around the rim, for example by a snap-fit engagement underneath a downwardly facing surface of such a flange part. The clamp part preferably comprises an upper wall part having the aperture therein, preferably a central aperture, with peripheral skirt walls extending downwardly therefrom and having  
30 snap-fit engagement parts thereon to engage with the vial, e.g. with the said flange.

If the closure part has the above mentioned upwardly convex shape, then preferably the upper wall and the upwardly convex part of the closure part are

profiled such that the upwardly convex part bulges above the adjacent upper surface of the upper wall. Preferably the upper surface and the upwardly convex part may be profiled to form a smooth convex shape.

5 The cover part is preferably engageable with the clamp part. For example the cover part may be engageable by snap-fit means with the upper wall, or skirt wall of the clamp part, or the junction between the upper wall and skirt wall. For example the cover part may comprise a cap having an upper wall and a peripheral skirt wall, and the skirt wall of such a cap may have a snap-fit engagement part adjacent its lower extremity, to engage with the clamp part. Such snap-fit means  
10 may comprise a ridge on the cover part and a corresponding groove on the clamp part, or vice versa.

The cover part preferably at least partly covers a central aperture in the clamp part to thereby cover the above-mentioned region of the closure part. The sealing ridge extends downwardly from the lower surface of the upper wall of the  
15 cover part which is adjacent to and above the closure part when the cover part is engaged with the clamp part. The sealing edge preferably has a generally triangular section as cut parallel to the up-down direction, so that the sealing edge comprises the apex of the triangle. The sealing edge preferably follows a ring-shaped, e.g. circular, oval or polygonal closed perimeter as viewed looking upwardly toward the  
20 lower surface of the upper wall of the cover part.

The part of the cover part which includes the sealing ridge is preferably made removable from the clamp part and/or vial as follows. Preferably the upper wall has a segment, e.g. a pie-slice segment of a generally circular upper wall, linked to the remainder of the upper wall and/or skirt wall by one or more thin,  
25 frangible link which can easily be severed to allow the segment to be sufficiently (partly or wholly) detached from the remainder of the cover part.

Suitably the cover part may be made by injection moulding of a plastics material, suitably of the same plastics material as the clamp part.

The present invention further provides a vial when fitted with a closure  
30 system as described herein.

In a further aspect of this invention it has also been found that the internal profile of the plug part of the closure part can be important in ensuring that minimal

liquid content remains trapped in the vial when liquid content is removed therefrom using a needle. Generally the plug part of a vial closure has an outward-facing neck-contacting surface which engages with the interior surface of the vial neck, typically being a cylindrically-shaped outer surface which when the closure is in place is  
5 against the cylindrical interior surface of the vial neck, and an interior-facing surface which is exposed to the interior of the vial, and which merges with the neck-contacting surface at the point where the interior-facing surface meets the interior surface of the vial neck. In known plug parts of the state of the art, for example as shown in EP-A-0956849 Fig. 4 and EP-A-0794129 when the closure is in place the  
10 interior-facing surface of the plug part encloses an angle of  $90^\circ$  or less with the interior surface of the vial neck. This results in the problem that due to capillary action and/or surface tension liquid content becomes trapped in this acute angle and cannot easily be removed using a needle. In a small vial a significant proportion of the content can become trapped in this way.

15 Therefore according to this further aspect of the invention a vial closure is provided having a plug part which has an outward-facing neck-contacting surface which engages with the interior surface of the vial neck when the closure is in place is against the cylindrical interior surface of the vial neck, and an interior-facing surface which is exposed to the interior of the vial and which when the closure is in  
20 place encloses an angle of greater than  $90^\circ$  with the interior surface of the vial neck.

Preferably this angle is in the range  $120-160^\circ$ , for example ca.  $135^\circ \pm 10^\circ$ .

This angle may be achieved by the outward-facing neck-contacting surface of the plug part being generally cylindrical, at least adjacent the lower end of the plug  
25 part, and by the interior-facing surface and the outward-facing neck-contacting surface forming an edge enclosing an angle less than  $90^\circ$  between them. Preferably this angle is in the range  $30-60^\circ$ , for example ca.  $45^\circ \pm 10^\circ$ . It will of course be appreciated that in practice when making the plug part of an elastomeric material using for example injection moulding it may be necessary for such an edge to  
30 deviate from a perfect knife edge, for example having a small radius of curvature, e.g. of 0.5mm or less, or a small flat.



When the interior-facing surface encloses an angle of greater than 90° with the interior surface of the vial neck in this aspect of the invention it is found that this minimises the tendency of surface tension and capillary effects to cause residual liquid content in the vial to become trapped between the closure and the interior surface of the vial.

The present invention also provides a method of filling a vial comprising: providing an assembly of an empty vial having a closure part and clamp part thereon;

inserting a filling needle downwardly through the upper wall of the closure part;

injecting a liquid medicament through the filling needle to fill the vial to a suitable extent;

withdrawing the needle to leave a residual puncture hole;

engaging a cover part with the clamp part.

Preferably prior to engaging the cover part a laser beam or other source of heat is directed at that part of the upper surface of the closure part where the puncture has occurred to melt the elastomer material in the immediate locality of the puncture, and to thereby seal the residual puncture hole.

The above-mentioned assembly may be supplied from a separate source, so as a further aspect this invention provides a pharmaceutical vial having a mouth opening closed by an elastomeric closure part shaped to sealingly engage with the mouth opening and having a lower surface facing the interior of the vial and an opposite upper surface facing away from the vial, and capable of being punctured by a needle, a clamp part engaged with the rim of the mouth opening, and able to bear upon the upper surface of the closure part to hold the closure part in a closing relationship with the mouth opening, the clamp part having an aperture therein through which a region of the upper surface of the closure part is exposed when the clamp part is engaged with the vial, the clamp part and/or vial being engageable with an at least partly removable cover part able to cover the said region of the closure part and being able to form an enclosure with the closure part.

In such a method, the automatic handling of a vial, e.g. a vial fitted with a closure system, or with the closure part and clamp part of a closure system as

described herein, on a conveyor system by means of which the vial may be transported to one or more station where an operation such as filling using a needle or laser-sealing the residual puncture site is facilitated by a vial construction which comprises a further aspect of this invention.

5           According to this further aspect a stand for a vial is provided comprising a ring-shaped stand having an inner perimeter such that the base of a vial may fit and be retained therein, the stand having an outer perimeter which extends, in a direction perpendicular to the mouth-base axis direction of a vial retained therein, beyond the outer diameter of the vial body. Such a stand preferably has upper and  
10   lower surfaces which are substantially flat and parallel. The invention also provides a combination of a vial having a base which can engage with the inner perimeter of such a ring-shaped stand, and such a stand. For example such a vial may have a base having an upper surface forming the bottom inner surface of the vial, and a lower surface from which extends downwardly an engagement part able to engage  
15   with the inner perimeter of such a stand. If the vial is to be transported on a conveyor system then to maintain a sterile environment it is normal to direct a downward flow of purified air over the conveyor and vials thereon. Such a stand can easily be gripped by gripping means on a conveyor, enabling the vial to be held such that the closure is uppermost and therefore upstream in the flow of air,  
20   minimising the risk of contamination of the closure with micro-organisms.

The invention will now be illustrated by way of example only with reference to the following drawings.

Fig. 1 shows a longitudinal section of a vial and vial closure system according to this invention cut along an up-down plane.

25           Fig. 2 shows a cover part of a closure system according to this invention viewed in various orientations.

Fig. 3 shows a perspective view of a vial having a closure part and a clamp part in place,

Fig. 4 shows a perspective view of the vial plus closure part and clamp part  
30   as shown in Fig. 3, with a cover part also in place.

Fig. 5 shows the vial plus closure part, clamp part and cover part of Fig. 4, with the cover part partly removed.

Fig. 6 shows a longitudinal section of a partly assembled vial and closure system of this invention.

- 10 vial
- 11 mouth opening
- 5 12 neck
- 13 rim, 13A upper surface, 13B lower surface
- 14 peripheral kerb 14
- 15 sealing ridge
- 16 vial base
- 10 17 integral engagement part
- 20 closure part
- 21 plug part, 21A interior of the plug part
- 22 outwardly extending flange
- 23 upper part of the closure part
- 15 24 upper wall, 24A central region
- 30 clamp part
- 31 upper wall
- 32 skirt wall
- 33 snap fit engagement parts
- 20 34 upper downward facing surface
- 35 lower downward facing surface
- 36 central circular aperture
- 37 groove
- 40 cover part
- 25 41 upper wall.
- 42 peripheral skirt wall
- 43 snap fit engagement parts
- 44 sealing ridge
- 45 sealed enclosure
- 30 46 removable segment of the upper wall and skirt wall of the cover part
- 47 thin severable links
- 50 ring-shaped stand

51 inner perimeter

52 outer perimeter

53 upper surface

54 lower surface

5 Referring to Fig. 1 a vial 10 is shown being of generally cylindrical shape.

At its upper end as shown the vial has a mouth opening 11, with a neck 12 immediately below. Larger capacity vials 10 may have a wider body section below their neck 12, as is well known in the art. The mouth opening 11 is surrounded by an outwardly extending rim 13 in the form of a flange having an upper surface 13A and a lower surface 13B. The upper surface 13A of flange 13 is bounded by a peripheral kerf 14. From upper surface 13A of flange 13 a sealing ridge 15 extends upwardly being of generally triangular section as cut along an up-down plane and of circular ring shape concentric with the cylindrical vial 10 in plan. The upper inner edge of the neck 12 is of a conical profile flaring upwardly, to guide the insertion of the plug part 21 (to be described) of the closure part 20.

Inserted into mouth opening 11 and extending some way down neck 12 is the plug part 21 of a closure part 20 made integrally of a thermoplastic elastomer material. The plug part 21 is a tight fit into the neck 12 to thereby form a close seal. The closure part 20 has an outwardly extending flange 22, of shape and dimensions such that flange 22 fits comfortably within kerf 14. The flange 22 has an upper surface and a lower surface. When the closure 20 is in position as shown in Fig. 1 the lower surface fits against the upper surface 13A of flange 13 and the sealing ridge 15 compresses and deforms the elastomer material of the lower surface of flange 22, contributing to a good seal between surfaces 13A and the lower surface of flange 22.

The plug part 21 is of generally cylindrical shape and has a hollow interior 21A. The upper part 23 of the closure part 20, centrally inward of flange 22 is upwardly convex, being of a frusto-conical shape having a flat upper surface. The upper part of the interior 21A of the plug part generally follows the upward convex shape of the upper part 23. The upper end of the cylindrical interior 21A is closed by an upper wall 24 which is thin enough to be punctured by a hollow needle (not shown) by which the vial 10 can be filled whilst the closure part 20 is in place.

A clamp part 30 holds the closure part 20 in place against the flange 13. The clamp part 30 comprises an upper wall 31 generally circular in plan, from the periphery of which downwardly extends a skirt wall 32. At the lower extremity of the skirt wall 32 is a snap fit engagement part 33, being a wedge shaped inwardly extending lip which can engage under the lower surface 13B of flange 13 to hold the clamp part 30 in place on the assembly of vial 10 and closure part 20. The clamp part 30 is made of a resilient plastics material to facilitate this. The clamp part 30 has two regions of downward facing surfaces, being an upper downward facing surface 34 and a lower downward facing surface 35 which bear respectively upon the upper surface of the upper wall 24 of the closure part 20 and upon the upper surface of the flange 22 to hold closure part 20 in place against flange 22.

In the upper wall 31 of the clamp part 30 is a central circular aperture 36, through which bulges the central convex part of the upper part 23 of closure part 20 so that a central region 24A of the upper wall 24 is exposed through the aperture 36. The profile of the upper surface of the clamp part is profiled so that the upper part 23 of closure part 20 projects in this way. The inner perimeter of the aperture 36, adjacent to the upper downward facing surface 24, is also shaped to correspond with the outer profile of the upper part 23 of the closure part 20.

Around the periphery of the upper wall 31 of the clamp part 30 is a groove 37 with which the cover part 40 engages.

The cover part 40 is in the form of a cap comprising an upper wall 41, with a peripheral skirt wall 42, at the lower extremity of which is a snap fit engagement part 43 being an inwardly directed wedge shaped lip, which can engage with the groove 37 on clamp part 30 to retain cover part 40 securely in place on clamp part 30. The cover part 40 is made of a resilient plastic material to facilitate this.

A lower surface of the upper wall 41 has a sealing ridge 44 extending downwardly therefrom. As seen looking upwards toward the lower surface this ridge 44 has a circular ring-shaped plan and is of a triangular section so that it terminates in a lower knife edge. As the cover part 40 is held in contact with the clamp part 30 by the snap-fit parts 43, 37 its resilience forces it against the central region 23A of the upper part 23 of the closure 20, and the ridge 44 engages with and compressibly deforms the elastomer of the central region 23A to thereby form a

seal with the region 23A. A sealed enclosure 45 is thereby formed between the cover part 40 and the closure part 20. The seal between the ridge 44 and the region 23A is sufficient that contaminants such as microorganisms, virus particles etc cannot pass the seal, so the enclosure 45 can remain sterile.

5           Figs. 2A-2E respectively show a plan view, a side view looking in the upward direction of Fig. 2A, and three perspective views of the cover part 40. As seen more clearly in Figs. 2, 3 and 4, whereas the lower part of the skirt wall 42 and its lip 43 extend in a continuous ring, a part 46 of the upper wall 41 of the cover part 40, including that part of the upper wall 41 which has the sealing ridge  
10   44 on its lower surface, is made as a segment which is connected to the remainder of the cover part 40 by thin severable links 47, being integrally made bridges of plastics material. The peripheral edge of this segment 46 may be lifted by a user as shown to thereby break the bridges 47, and to lift the segment 46 from the closure part 20. This breaks the seal between the ridge 44 and the central region 24A of the  
15   upper wall 24 of the closure part 20 and exposes the central region 43A, leaving the cover part 40 retained on the clamp part 30 by the snap fit lip 43 of skirt wall 42.

          The vial 10 and closure system 20, 30, 40 may be used as follows. An assembly of an empty vial 10, closure part 20 and clamp part 30 is provided as shown in Fig. 6. This assembly may be sterilised by appropriate generally known  
20   methods either before (i.e. as separate parts) or after assembly. In a sterile environment such as a flow of sterile air, a filling needle (not shown) may then be inserted downwardly through the upper wall 24 of the closure part 20, and a liquid medicament injected therethrough to fill the vial 10 to a suitable extent. Known  
25   filling needles suitable for this purpose may also have an air exit channel to release displaced air from the interior of vial 10. When the vial 10 has been filled in this manner the needle is withdrawn. The elastomer material of the wall 24 closes around the residual puncture hole (not shown) in closure part 20, and whilst still in the sterile environment a laser beam or other source of heat is directed at that part of the upper surface of the wall 24 where the puncture has occurred to melt the  
30   elastomer material in the immediate locality of the puncture, and to thereby seal the residual puncture hole. Then, still in the sterile environment, the cover part 40 may be engaged with the clamp part as shown in Fig. 1.

Immediately prior to use of the medicament the segment 46 is lifted as described above, and an injection needle attached to a syringe (not shown) may be inserted through the central region 24A, in the normal manner of using a vial closed with an elastomeric closure.

5        Because the central region 24A has been maintained in the sterile enclosure 45 until the segment 46 is lifted, there is no need for the user to give the region of the closure part 20 to be punctured, i.e. the region 24A, a wipe with a sanitising agent as would be necessary with prior art vial closure systems.

10        Figs. 1-6 show a relatively small capacity vial 10 of an overall cylindrical profile. For stability and to assist automated handling the base 10A of the vial 10 is mounted in a ring-shaped stand 50 extending outwardly from the overall cylindrical shape of the vial 10 at its base. The stand 50 has an inner perimeter 51 such that the base of the vial 10 may fit and be retained therein, and has an outer perimeter 52 which extends, in a direction perpendicular to the mouth-base axis direction of the  
15        vial retained therein 10, beyond the outer diameter of the vial body. The stand 50 has upper 53 and lower 54 surfaces which are substantially flat and parallel. The vial 10 itself has a base 16 having an upper surface forming the bottom inner surface of the vial 10, and a lower surface from which extends downwardly an integral engagement part 17 able to engage in a tight friction or snap fit with the inner  
20        perimeter 51 of the stand 50.

      Fig. 1A shows in detail the part of Fig. 1 adjacent to the lower end of the plug part 21 and illustrates a further aspect of this invention in which the plug part 21 has an outward-facing neck-contacting cylindrical surface 21B, which when the closure 21 is in place is against the cylindrical interior surface 12A of the vial neck  
25        12. The closure 21 also has an interior-facing surface 21C which is exposed to the interior of the vial, and which as seen in Fig. 1 when the closure is in place encloses an angle "A" of greater than 90°, being ca. 135°, with the interior surface 12A of the vial neck 12.

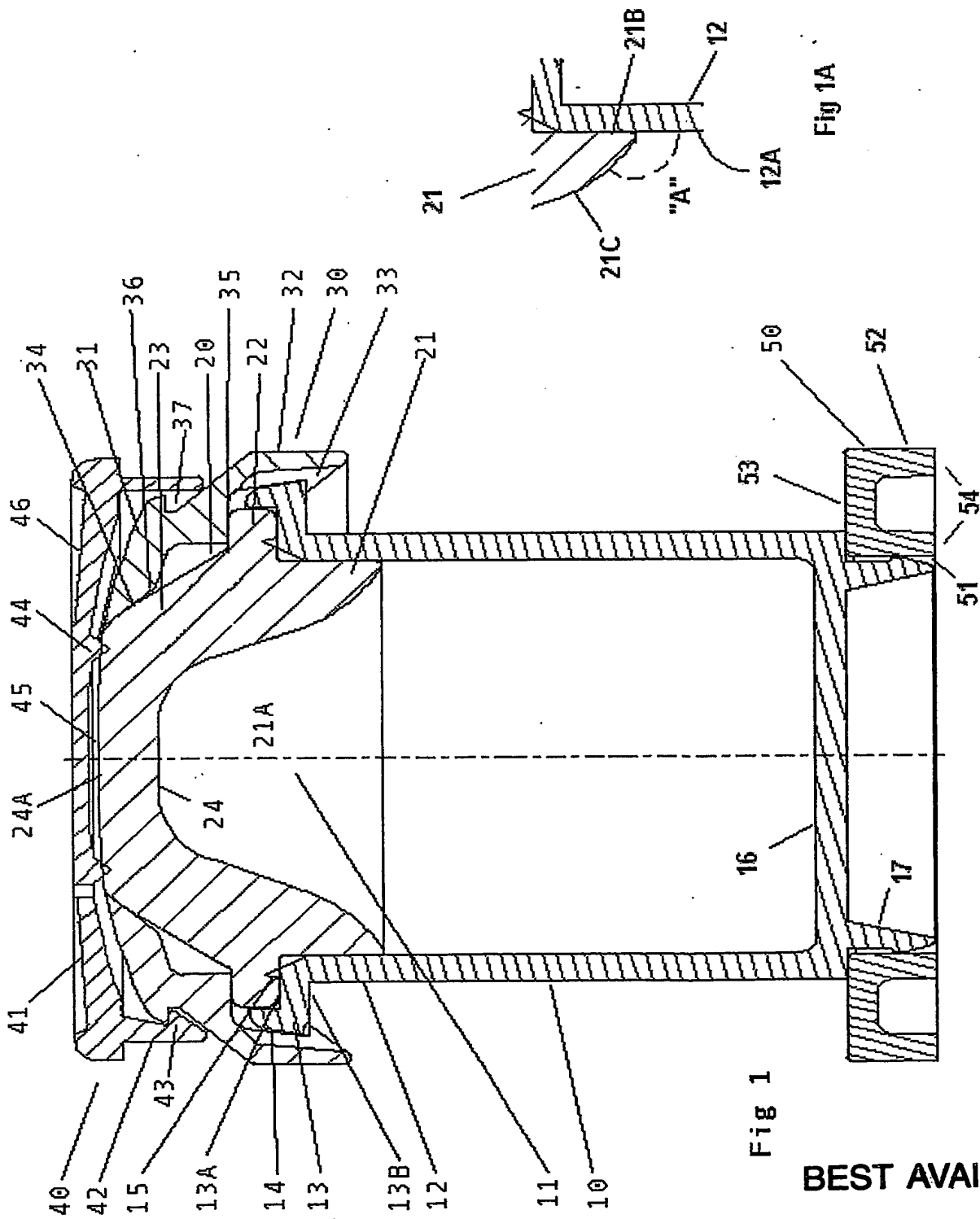
      This angle "A" is achieved by the outward-facing neck-contacting surface  
30        21B of the plug part 21 being generally cylindrical adjacent the lower end of the plug part, and the interior-facing surface 21C and the outward-facing neck-contacting surface 21B forming an edge enclosing an angle ca. 45° between them.

It is found that this profile of the plug part minimises the tendency of surface tension and capillary effects to cause residual liquid content in the vial to become trapped between the closure and the interior surface of the vial. To assist the cylindrical plug part 21 in fitting into the vial neck 12, the vial neck 12 may have a slightly conical profile, being slightly wider at its upper mouth opening than adjacent the lower end of the plug part.



**Claims.**

1. A vial closure having a plug part which has an outward-facing neck-  
contacting surface which engages with the interior surface of the vial neck when the  
5 closure is in place is against the cylindrical interior surface of the vial neck, and an  
interior-facing surface which is exposed to the interior of the vial and which when  
the closure is in place encloses an angle of greater than  $90^\circ$  with the interior surface  
of the vial neck.
- 10 2. A vial closure according to claim 1 wherein the angle is in the range  $120^\circ$ -  
 $160^\circ$
3. A vial closure according to claim 2 wherein the angle is  $135^\circ \pm 10^\circ$ .
- 15 4. A vial closure having a plug part which has an outward-facing neck-  
contacting surface which engages with the interior surface of the vial neck when the  
closure is in place is against the cylindrical interior surface of the vial neck, and an  
interior-facing surface which is exposed to the interior of the vial and wherein the  
outward-facing neck-contacting surface of the plug part is cylindrical, at least  
20 adjacent the lower end of the plug part, and the interior-facing surface and the  
outward-facing neck-contacting surface form an edge enclosing an angle less than  
 $90^\circ$  between them.
5. A vial closure according to claim 4 wherein the angle is in the range  $30^\circ$ - $60^\circ$ .
- 25 6. A vial closure according to claim 5 wherein the angle is  $45^\circ \pm 10^\circ$ .



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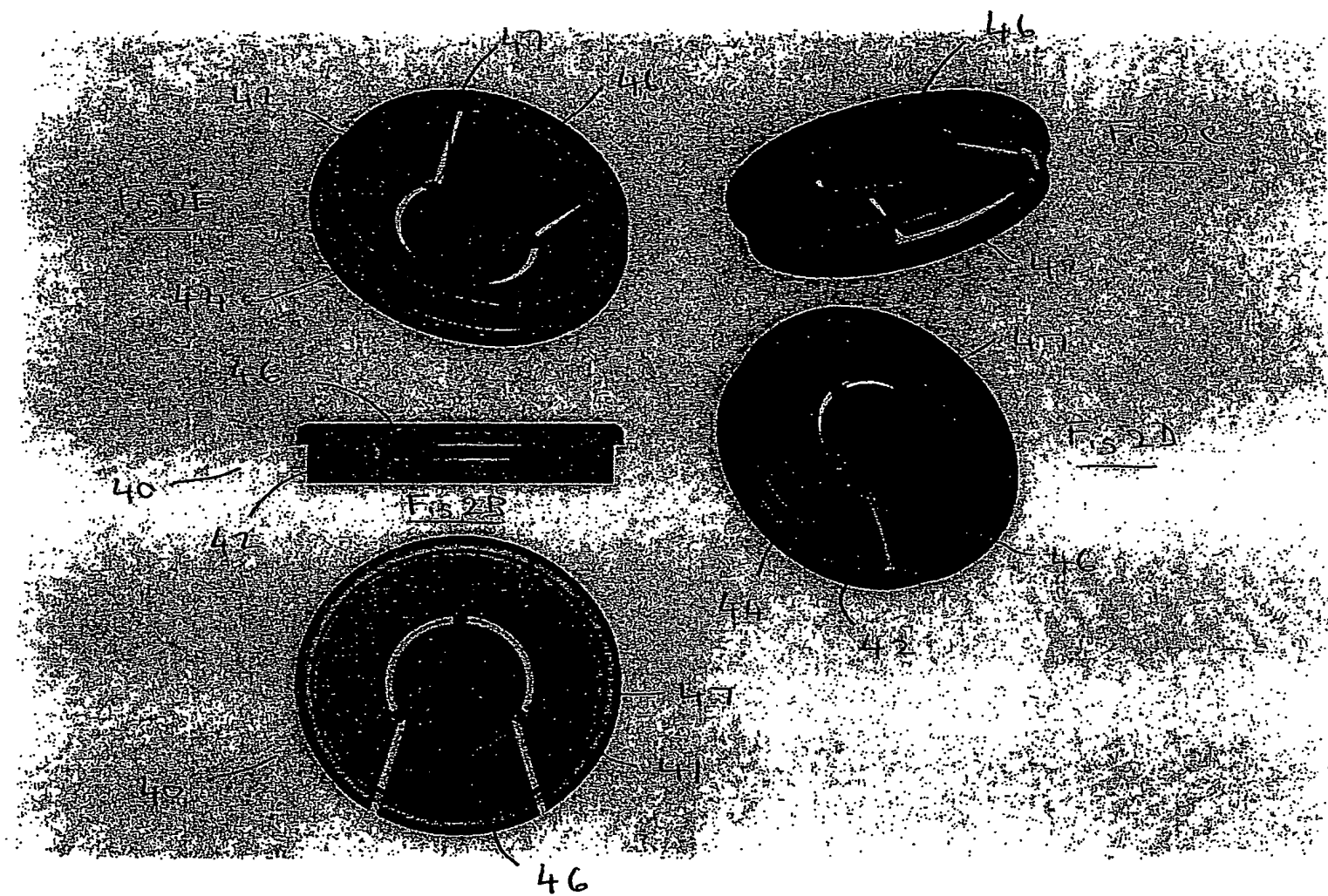


Fig. 2A

Fig. 2

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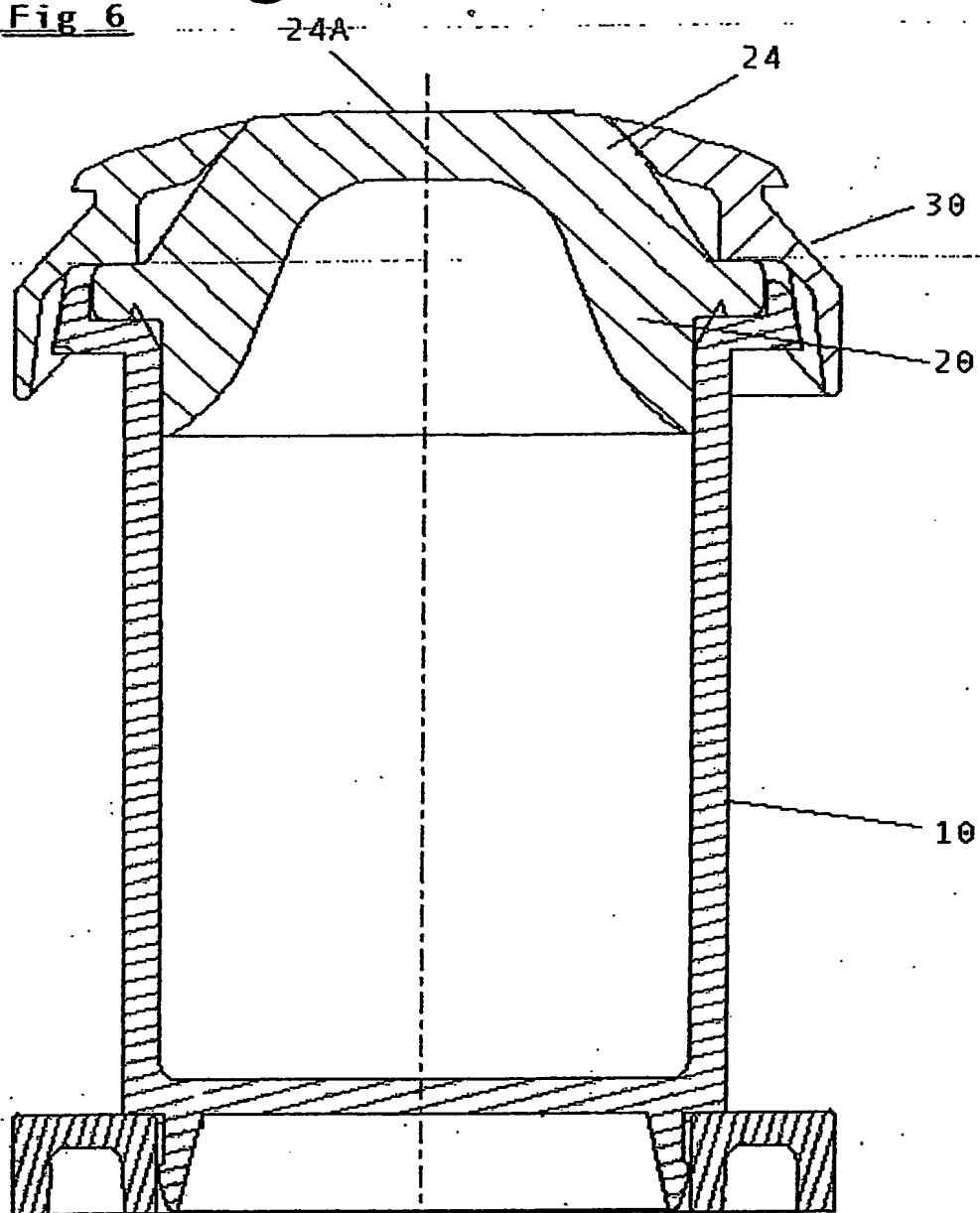
Fig. 3

Fig. 4

Fig. 5

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Fig 6



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